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Professor Pangloss and the Pangenome: Does *Staphylococcus aureus* Have the Best of All Possible Worlds?

In Voltaire's 1759 novel *Candide*, the eponymous hero is indoctrinated by his tutor, Professor Pangloss, to believe that "everything is for the best in the best of all possible worlds." In this issue of the *Journal*, Long and colleagues (pp. 1127–1137) present a meticulous and detailed analysis of whole genome sequencing data of 1,382 isolates of *Staphylococcus aureus* from 246 children with cystic fibrosis (CF), attending five U.S. care centers (1). The authors suggest that *S. aureus*, through access to an open pangenome (the collective genetic content of all isolates), develops persistent genotypes, well adapted to the CF lung. For *S. aureus*, this may indeed be "the best of all possible worlds." The authors offer us some intriguing insights into how *S. aureus* achieves this and the implications this may have for the patient with CF.

In the first account of CF, Dorothy Andersen described "... plugging of the lumens of most if not all of the bronchi with tenacious, greenish-gray mucopurulent material ..." (2). We now know that these appearances result from dysfunction of the CF transmembrane conductance regulator, leading to viscid

respiratory secretions, failure of the mucociliary escalator, bacterial infection, and bronchiectasis (3). In a subsequent article (4), Andersen described the microbiology of CF as, "Cultures taken early in the course of the disease grow *S. aureus* hemolyticus in nearly every case. ..." Contemporary registry data support the high prevalence of *S. aureus* early in life, but suggest that the organism is present in over half of individuals with CF well into the fourth decade (5). Long and colleagues describe some of the secrets behind the organism's remarkable longevity in the CF airway.

Almost half of the 246 children studied were infected with multiple, coexisting *S. aureus* lineages, often with different antibiotic susceptibility profiles. The authors show that these infections were more often concurrent than they were sequential. Multiple lineages of *S. aureus* do not primarily arise from hypermutation of resident organisms in the CF airway—mutation rates in this study were comparable to other patient groups. Mutations in the *agrA* and *rsbU* transcriptional regulators, well recognized as important mediators of the acute–chronic transition in *S. aureus*, were common in *S. aureus* isolates in this study and were confirmed to modulate virulence through altered protease production and hemolysis.

But the ability to interrogate relationships between pathogen genotype and patient history in this large cohort adds interesting new detail to the picture of how persistent infection is established. Mutations in *thyA*, which confer resistance to trimethoprim-sulfamethoxazole, were associated with the patient being treated

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with this specific antimicrobial. In addition to trimethoprim-sulfamethoxazole resistance, *thyA* mutation has been associated with a switch to the small colony variant phenotype, which results in generally increased antibiotic tolerance and *in vivo* persistence (6). In contrast, *rpoB*, mutations in which confer resistance to rifamycin, had the strongest signature of natural selection in the study, despite the fact that only a minority of patients with *de novo* mutations in this gene were exposed to this drug. Mutations in *rpoB* have previously been associated with *S. aureus* persistence through increased tolerance of mammalian antimicrobial peptides (7). Thus, antibiotic-mediated selection for resistance may also confer a general survival advantage in the CF airway (*thyA*), and, conversely, selection for increased survival in the CF airway may have the byproduct of resistance to an antibiotic (*rpoB*) that the organism has not yet encountered.

The data presented by Long and colleagues raise an important question about microbial ecology: How spatially structured are the diverse *S. aureus* populations within the lungs of people with CF? There is good evidence for spatial structuring of microbial populations across the CF lungs (8), and the degree of intermixing (or not) of *S. aureus* subpopulations will be key in understanding the selection of persisting strains. Do different strains of *S. aureus* coexist side by side or do they rarely meet? This may also resolve some open questions about how *S. aureus* lives in CF lungs: are some or all populations intracellular (9), associated with the bronchiolar tissue surface (10), or living within mucus in the bronchial lumen (11)?

This study not only provides insights into the lifestyle of *S. aureus* but also suggests practical conclusions for infection prevention and control. Using granular molecular epidemiology, Long and colleagues provide detailed information on 11 paired cases in which “strain sharing” between individuals with CF is likely (isolates were separated by ≤ 36 variants). Strain sharing may be explained by sibling pairs (5 pairs). However, for several pairs attending different CF centers, acquisition of the organism appeared after contact with a single care provider who moved from one CF center to another. Around one-third of the U.S. population will carry *S. aureus* in the nasopharynx (12). These data underscore the need for scrupulous adherence to infection prevention and control guidelines (13).

The data on antimicrobial resistance are important for clinical practice. In the United Kingdom, but not in the United States (14), it is standard practice to use prophylactic antistaphylococcal antibiotics in young infants with CF from diagnosis (15). As noted above, children in this study could be infected simultaneously with multiple, different *S. aureus* lineages. One individual might harbor both methicillin-resistant *S. aureus* (MRSA) and sensitive strains. Indeed, lineages could change from methicillin-resistant to methicillin-sensitive over time. This suggests that culture and sensitivity techniques, currently used in CF centers, may not be sufficiently comprehensive for optimal treatment of MRSA. The authors propose that routine laboratory tests might be developed to characterize coexisting *S. aureus* lineages better, using either culture or whole genome sequencing. Furthermore, long-term surveillance may be necessary before successful eradication of MRSA can be claimed. The STaph Aureus Resistance - Treat Or Observe (STAR-too) trial of MRSA eradication (16) reported 82% eradication at 28 days, dropping to 54% at 84 days.

Finally, the authors suggest that new antimicrobial agents might be designed to reduce the virulence of the organism without exerting selective pressure for resistance, and such agents have been proposed as useful “antibiotic adjuvants” (17). Voltaire’s novel *Candide* contains an incident (based on historical fact) in which a British Admiral is shot by firing squad “to encourage the others.” *Candide* is a satire—it is plainly ridiculous to expect survivors to be encouraged by the execution of one of their number—or is it? In the field of antimicrobial resistance, the execution of bacteria, with an antimicrobial, exerts selective pressure and “encourages” bacterial resistance. Long and colleagues have described an organism exquisitely adapted for long-term survival in the CF airway. New approaches are needed to combat *S. aureus* infection as it enjoys “the best of all possible worlds.” ■

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It's Not Just a Smoking-related Disease: Outdoor Pollution May Increase Risk of Chronic Obstructive Pulmonary Disease

It is well accepted that air pollution exacerbates existing respiratory diseases in adults, including asthma and chronic obstructive pulmonary disease (COPD). It is less clear if cumulative exposure to air pollution increases the incidence of new obstructive lung diseases in adults. In this issue of the *Journal*, Shin and colleagues (pp. 1138–1148) present a population-based study of all 5 million adults living in the Canadian province of Ontario who were free of asthma or COPD diagnosis in 2001 (1). During the 15-year study follow-up period, over 340,000 incident cases of COPD and over 218,000 incident cases of asthma were identified. Using a 3-year average of air pollution exposure with a 1-year lag, the authors found that multiple outdoor pollutants, including fine particulate matter (PM_{2.5}), nitrogen dioxide (NO₂), and ozone (O₃), were associated with greater COPD incidence, which is defined as a COPD hospitalization or at least three physician claims for COPD within 2 years. In contrast, there were no associations between exposure to these pollutants and new adult-onset asthma.

Ontario is a large contiguous geographic area that includes a large metropolitan area and more rural areas with sufficient variability in the long-term exposure to these pollutants to examine associations with asthma and COPD incidence, even at the relatively low pollution concentrations in Canada. A major strength of this population-based cohort study is that it included *all* Ontarians with minimal concern for selection bias because everyone is eligible for the publicly funded health plan. However, the use of administrative claims data has the important limitation that the authors could not directly adjust for individual-level habits such as tobacco use, which is the number one cause of COPD. The authors attempted to address this limitation by adjusting for individual-level comorbidities, fine-scale neighborhood characteristics, and indirectly adjusted for smoking and obesity using an auxiliary dataset. The findings for COPD were robust to

adjustment for these potential confounding variables. Interestingly, healthier adults (those without comorbidities and those who were younger at baseline) had a larger relative risk of COPD in association with pollution than those who had more comorbidities or were older. As in other research on the health effects of pollution, residents in neighborhoods of lower socioeconomic position had a heightened risk of COPD incidence in association with PM_{2.5} compared with those in more privileged neighborhoods.

The authors examined the shape of exposure–response relationships and found “supralinear functions” for PM_{2.5}, O₃, and the redox-weighted oxidative potential of O₂ and NO₂, meaning that the exposure–response relationship for COPD incidence was steeper at lower exposure concentrations (<10 μg/m³ PM_{2.5} and <40 ppb O₃) and less steep at higher exposure concentrations. This pattern of greater health effects per increment of pollution at the lower range of exposure has been observed for other health effects of PM_{2.5} and O₃ exposure, including mortality (2). For NO₂ exposure, there appeared to be a threshold effect with increasing risk for COPD only above 25 ppb. The authors importantly highlight that these adverse effects were observed for concentrations well below the current U.S. national ambient air quality standard for PM_{2.5}, O₃, and NO₂. Several recent reports have concluded that despite the strong plausibility that outdoor pollution causes COPD (based in part on the compelling evidence for tobacco and indoor biomass smoke), the evidence thus far has been deemed insufficient to determine causality (3–5). This study provides compelling evidence that long-term exposure to higher concentrations of ambient pollution increases the incidence of COPD.

In contrast, results for adult-onset asthma were null. There are several possible reasons for these null results: 1) there is truly no effect of air pollution during adulthood on adult-onset asthma at the pollution concentrations observed; 2) sampling error, which randomly resulted in variation from the true population effect; or 3) bias was present in the study that only (or more severely) impacted the asthma analysis and not the COPD analysis. We discuss each of these below.

Air pollution exposure may not increase the risk of asthma in adults at the concentrations observed in this study. A recent American Thoracic Society workshop concluded that traffic-related

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